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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/269,321	09/13/99	KAELIN JR.	W 46793

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RONALD I EISENSTEIN
NIXON PEABODY
101 FEDERAL STREET
BOSTON MA 02110

EXAMINER	
SANDALS,W	
ART UNIT	**PAPER NUMBER**
1636	12

DATE MAILED: 11/08/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/269,321	Applicant(s) Fine et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Aug 23, 2000* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *15-27* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *15-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. Amendments to the specification in Paper No. 11 has been considered and not found persuasive regarding the rejection of claims 15-26 under 35 USC 112, first paragraph, scope of enablement, in the previous office action, and the rejection is sustained. Response to the arguments is contained in the repeated rejection below.

2. Arguments filed in Paper No. 11 regarding the rejection of claims 15, 25 and 26 under 35 USC 102(e) have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

3. Arguments filed in Paper No. 11 regarding the rejection of claims 15-23, 25 and 26 under 35 USC 103(a) have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Base claim 25 contains newly amended language which states at line 8 "encodes a protein that stimulates production", and then at line 9 "encodes a gene that inhibits production". There is no support in the originally filed specification for this language, and as such it constitutes new matter.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 15-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cells *in vitro*, does not reasonably provide enablement for cells in an animal, *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification contains references to methods of gene therapy, and the claims are drawn to a method of selectively targeting a malignant cell. While applicants have shown examples of targeting a malignant cell *in vitro*, they have not demonstrated any method of

targeting a malignant cell *in vivo*. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve developing a gene therapy method.

b- Examples have been provided which show the introduction of a vector into normal rat brain tissue, and some *in vitro* examples of the method. However, no examples of gene therapy have been demonstrated, and the application provides only limited, prophetic teachings on the method of targeting a malignant cell *in vivo*.

d- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and

unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

f- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

g- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

9. Arguments set forth in Paper No. 11 assert that "if claims are enabled for one use, no further inquiry is needed". To the contrary, a claim must be enabled for its intended use.

10. Arguments set forth in Paper No. 11 assert that the references used in the above rejection discuss **"clinical efficacy"**, not enablement. The arguments set forth above demonstrate that gene therapy is not enabled, especially as shown in the quote from Anderson.

11. Arguments set forth in Paper No. 11 assert that the *in vitro* and *in vivo* examples taught in the instant specification demonstrate enablement. The instant examples do not show a method of treatment, but teach that certain aspects of the invention such as "activity of a transfected gene in

cells", which has already been stated in the above scope of enablement rejection is enabled. As such, the examples do not overcome the instant rejection.

12. No response has been given to other arguments which do not address claims limitations or rejections.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 15-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claim 25 recites, at line 12, "selectively expressing the gene by the E2F in said cell". This language is not entirely clear as to how the E2F acts to "selectively express". The concept of "selective expression" has not been introduced earlier in the claim. No mechanism of action for "selective expression" has been explicitly stated, and as such is unclear as to the meaning of the term.

16. Claims 19 and 25 are rejected as being unclear since the term "negative potentiator" (and "positive potentiator") is not an art recognized term and "negative potentiator" (and "positive potentiator") is not defined in the claims or specification.

17. Claim 20 is rejected as being unclear because the term "dominant negative mutant"is not defined in the claims or specification.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

19. Claims 15, 25 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 5,885,833.

US Pat No. 5,885,833 taught (see especially the abstract, the summary, and columns 5-8 and 11-21) the transfecting of a glioma cell with a viral vector (which may be an adeno-associated viral vector) or a plasmid which comprised an E2F responsive DHFR, Pol alpha, BMyb or cMyc promoter or E2F enhancer element which controls expression of an activator sequence, which may be a TK gene or a cytotoxin (see column 12).

Response to Arguments

20. Arguments set forth in Paper No. 11 assert that the "selective" targeting and expressing of the instant claimed E2F promoter is not anticipated by US Pat No. 5,885,833. On the contrary, the E2F promoter of US Pat No. 5,885,833 inherently contains all of the properties of the instant claimed E2F promoter.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 15-23 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raj et al. or Xiao et al. or US Pat No. 5,885,833 in view of WO 94/18992 and US Pat No. 5,529,774.

Raj et al. taught (see especially the abstract, the introduction, page 1281, column 2 and the figures) the transfecting of a glioma cell with a plasmid which comprised an E2F responsive

Xiao et al. taught (see especially the abstract and page 697, column 1 and the figures) the transfecting of a glioma cell with a plasmid which comprised an E2F responsive promoter.

US Pat No. 5,885,833 taught the invention as described above.

Raj et al. or Xiao et al. or US Pat No. 5,885,833 did not teach that the viral vector was an adenovirus vector or a herpes virus vector.

WO 94/18992 taught (see especially the abstract and page 27) the advantageous use of an adenoviral vector to deliver a thymidine kinase gene to tumor cells, which may be glioma cells.

US Pat No. 5,529,774 taught the advantageous use of retroviral vectors to deliver a thymidine kinase gene to glioma cells.

Since the claims also read on *in vitro* applications of the method, it would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the method of transfecting of a glioma cell with a viral vector or plasmid which comprised an E2F responsive DHFR, Pol alpha, or cMyc promoter or E2F enhancer element as taught by each of Raj et al. or Xiao et al. or US Pat No. 5,885,833 with the adenoviral or retroviral vectors of WO 94/18992 and US Pat No. 5,529,774 because WO 94/18992 and US Pat No. 5,529,774 taught the advantageous and well known use of viral vectors to transfect a target cell, where the viral vector comprised a thymidine kinase cytotoxic gene.

One of ordinary skill in the art would have been motivated at the time of filing of the instant application to combine the method of transfecting of a glioma cell with a viral vector or plasmid which comprised an E2F responsive DHFR, Pol alpha, or cMyc promoter or E2F enhancer element as taught by each of Raj et al. or Xiao et al. or US Pat No. 5,885,833 with the adenoviral or retroviral vectors of WO 94/18992 and US Pat No. 5,529,774 because US Pat No. 5,885,833 taught the advantageous use of viral vectors to practice the method, and WO 94/18992 and US Pat No. 5,529,774 taught the advantageous and well known use of viral vectors to transfect a target cell, where the viral vector comprised a thymidine kinase cytotoxic gene. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Raj et al. or Xiao et al. or US Pat No. 5,885,833 with WO 94/18992 and US Pat No. 5,529,774.

Response to Arguments

23. Arguments set forth in Paper No. 11 assert that the expression of the E2F promoter in malignant cells is not obvious. As stated in the response to the anticipatory rejection above, the properties of the E2F promoter are inherent, and must be possessed by the E2F promoter of the prior art.

Conclusion

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

25. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.

Examiner

November 5, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

09/269 231
Att # 12

1. Document ID: US 6117638 A

L5: Entry 1 of 35

File: USPT

Sep 12, 2000

US-PAT-NO: 6117638
DOCUMENT-IDENTIFIER: US 6117638 A
TITLE: Methods to screen for transcription factor-coactivator interactions
DATE-ISSUED: September 12, 2000

US-CL-CURRENT: 435/6; 435/29

APPL-NO: 9/ 054238
DATE FILED: April 2, 1998

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application claims the benefit of U.S. Provisional
Application Ser. No. 60/043,059, filed Apr. 4, 1997.

IN: Kushner; Peter J., Webb; Paul, Uht; Rosalie M.

AB: This invention provides methods for modulating gene expression at the
transcriptional level. In particular, the methods involve tethering a transcriptional
coactivator to a DNA binding domain that is specific for a target nucleic acid sequence and
contacting the coactivator with a transcription factor. The transcription factor triggers or
represses transcription mediated by the coactivator. Methods for identifying compounds that
are able to modulate gene expression are also provided.

2. Document ID: US 6080575 A

L5: Entry 2 of 35

File: USPT

Jun 27, 2000

US-PAT-NO: 6080575
DOCUMENT-IDENTIFIER: US 6080575 A
TITLE: Nucleic acid construct for expressing active substances which can be activated by
proteases, and preparation and use
DATE-ISSUED: June 27, 2000

US-CL-CURRENT: 435/320.1; 435/456, 435/464, 536/23.1

APPL-NO: 9/ 008308
DATE FILED: January 16, 1998

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
DE
197 01 141
January 16, 1997

IN: Heidtmann; Hans Heinrich, Mueller; Rolf, Sedlacek; Hans-Harald

AB: The invention relates to a nucleic acid construct for expressing an active
substance which is activated by an enzyme which is released from mammalian cells, which
construct comprises the following components: a) at least one promoter element, b) at least
one DNA sequence which encodes an active compound (protein B) c) a least one DNA sequence
which encodes an amino acid sequence (part structure C) which can be cleaved specifically by
an enzyme which is released from a mammalian cell, and d) at least one DNA sequence which
encodes a peptide or protein (part structure D) which is bound to the active compound
(protein B) by way of the cleavable amino acid sequence (part structure C) and inhibits the
activity of the active compound (protein B), and also to the use of the nucleic acid
construct for preparing a drug for treating diseases.

3. Document ID: US 6080578 A

L5: Entry 3 of 35

File: USPT

Jun 27, 2000

US-PAT-NO: 6080578
DOCUMENT-IDENTIFIER: US 6080578 A
TITLE: Cytopathic adenoviral E1B mutated viruses for therapy and prophylaxis of neoplasia
DATE-ISSUED: June 27, 2000

US-CL-CURRENT: 435/325; 435/320.1, 536/23.72

APPL-NO: 8/ 986331
DATE FILED: December 8, 1997

PARENT-CASE:
This application claims priority from U.S. Provisional Application Ser. No. 60/034,615, filed
Dec. 31, 1996.

IN: Bischoff; James R., Nye; Julie, Ng; Lelia, Horn; Sharon, Williams; Angelica,
Kim; David

AB: Methods and compositions for treating neoplastic conditions by viral-based
therapy are provided. Mutant virus lacking viral proteins which bind and/or inactivate p53
or RB are administered to a patient having a neoplasm which comprises cells lacking p53
and/or RB function. The mutant virus is able to substantially produce a replication
phenotype in neoplastic cells but is substantially unable to produce a replication phenotype
in non-replicating, non-neoplastic cells having essentially normal p53 and/or RB function.
The preferential generation of replication phenotype in neoplastic cells results in a
preferential killing of the neoplastic cells, either directly or by expression of a
cytotoxic gene in cells expressing a viral replication phenotype.